UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

24353 7590 02/17/2004

BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER	
GUZO, DAVID	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/17/2004

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,380	11/28/2000	Vincent J. Miles	7960-147	9424

TITLE OF INVENTION: METHOD FOR SELECTIVE INACTIVATION OF VIRAL REPLICATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	$1330	05/17/2004

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status is changed, pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above and notify the United States Patent and Trademark Office of the change in status, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check the box below and enclose the PUBLICATION FEE and 1/2 the ISSUE FEE shown above.

☐ Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 11/03) Approved for use through 04/30/2004.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

or Fax **(703) 746-4000**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

24353 7590 02/17/2004

BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,380	11/28/2000	Vincent J. Miles	7960-147	9424

TITLE OF INVENTION: METHOD FOR SELECTIVE INACTIVATION OF VIRAL REPLICATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	$1330	05/17/2004

EXAMINER	ART UNIT	CLASS-SUBCLASS
GUZO, DAVID	1636	435-005000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent); ❑ individual ❑ corporation or other private group entity ❑ government

4a. The following fee(s) are enclosed:

❑ Issue Fee

❑ Publication Fee

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s):

❑ A check in the amount of the fee(s) is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

Director for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date)

NOTE; The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMIT THIS FORM WITH FEE(S)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,380	11/28/2000	Vincent J. Miles	7960-147	9424

24353 7590 02/17/2004

BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER	
GUZO, DAVID	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/17/2004

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) system (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (703) 305-1383. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (Rev. 11/03) Approved for use through 04/30/2004.

Notice of Allowability	Application No.	Applicant(s)	
	09/724,380	MILES ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the amendment filed 11/13/03*.

2. ☒ The allowed claim(s) is/are *3,8-10,18 and 19*.

3. ☒ The drawings filed on *28 November 2000* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *1* .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

Examiner's Amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with James S. Keddie on 2/2/04.

The application has been amended as follows:

In the **Specification**:

Replace the Brief Description of Figure 1 on Page 17 with the following:

Figure 1 shows the terminal stem, central domain, and apical stem loop of adenovirus VAI RNA (SEQ ID NO:19) (Ma, Y. and M. B. Mathews. 1993. Comparative analysis if the structure and function of adenovirus virus associated RNAs. J. Virol. 67:6605-6617).

Please replace the Brief Description of Figure 2 on Page 17 with the following:

Figure 2 shows the antisense VA (ava) oligodeoxynucleotide species ava1, ava2, ava3 and ava9 annealed to complementary sequences of VAI RNA (SEQ ID NO:20).

Please replace the Brief Description of Figure 3 on Page 17 with the following:

Figure 3 shows the sequences of antisense species and complementary VAI RNA regions (SEQ ID NO:21-30), i.e., VAI RNA antisense oligodeoxynucleotides (ODN).

Please replace the Brief Description of Figure 5 on Pages 17-18 with the following:

Figure 5 (Parts A-C) shows human rhinovirus 14 5' NTR sequence and predicted secondary structure (SEQ ID NO:31) (Le, S. –Y., and Zuker, M. (1990) J. Mol. Biol. 216, 729-741). The initiating AUG start codon for the polyprotein, at nucleotide ("nt") 625, is shown as a shaded box, non-initiating AUG codons are shown as clear boxes. The YnXmAUG motif found in all picornavirus IRES elements and the 21-base conserved sequence found in all rhinovirus and enterovirus IRES elements are underlined. Nucleotide positions on the rhinovirus genome are marked by numbers.

Please the paragraph beginning on line 7 on Page 57 with the following:

Three tryptic peptides derived from purified p58 protein were sequenced by microsequencing. One of the sequences (AEAYLIEEMYDEAIGDYETA) (SEQ ID NO:11) was used to design a degenerate oligonucleotide probe (5'-GAA(G)GAA(G)ATGTAT(C)GAT(C)GAA(A)GC-3') (SEQ ID NO:12). This was used screen a cDNA library from the MDBK cell line made in the Lambda Zap II vector

(Stratagene). Duplicate plaque transfers were made to nylon filters (Hybond-N; Amersham, Arlington Heights, IL). Filters were than prehybridized in 6xSSPE (1xSSPE=0.18 M NaCl/10mM $NaPO_4$, pH 7.4, 1mM EDTA, 1% SDS, 0.2%Ficoll, 0.2% bovine serum albumin, 0.2% polyvinylpyrrolidone), 100μg of sonicated and denatured salmon sperm DNA per ml at 38°C for 4 hours and hybridized with ^{32}P-5'-end-labeled probe in 6xSSPE, 1% SDS, 100μg of sonicated and denatured salmon sperm DNA per ml for 38°C for 20 hours. Filters were washed in 6xSSPE, 1% SDS twice at room temperature for 10 minutes, once at 38°C for 15 minutes and exposed at –70°C with Kodak X-Omat film with enhancing screens. Positive phage plaques were identified and purified by further rounds of plaque hybridization. The pBluescript plasmid (Stratagene) was excised out *in vivo* according to the manufacturer's instructions. *Eco*RI fragments from 4 positive clones were analyzed by Southern blot hybridization using the degenerate oligonucleotide probe p58-3-2 (5'-GCIGTT(C)TCA(G)TAA(G)TCT(C)TG-3' (SEQ ID NO:13); I represents inosine) corresponding to the antisense-strand of a partial amino acid sequence (QDYETA) (SEQ ID NO:14) of the p58. One positive clone containing an insert of 1400 bp was obtained and analyzed by restriction enzyme mapping. After cloning into M13 mp18 and M13 mp19, the sequence of the p58 cDNA was determined by the dideoxynucleotide chain-termination method using Sequenase 2.0 (United States Biochemical). See SEQ ID No.17. Sequence data were analyzed using the Genetics Computer Group (GCG) sequence-analysis program (version 7.0).

Please replace the paragraph beginning on line 7 of Page 58 with the following:

The initial clone isolated contained a long open-reading frame but no termination codon, suggesting that the 3'-end was missing. The missing 3' end region was isolated using RACE-PCR (Rapid Amplification of cDNA ends-polymerase chain reaction) as described (Innis, et al., 1990). MDBK poly (A)+mRNA (1 μg) was reverse-transcribed using a hybrid primer (5'-GACTCGAGGATCCGAATTC-$(T)_{17}$-3') (SEQ ID NO:15). The cDNA pool was amplified by RACE-PCR in the presence of adapter primer (5'-GACGCGACCATCCGAATTC-3) (SEQ ID NO:16) and p58 gene-specific primer P58-5 (5'GCTGAAGAGCTCATCAAAG-3') (SEQ ID NO:17) under the conditions as described (Innis et al., 1990). After identifying the amplified product by Southern blot, the product was isolated from an agarose gel and cloned into M13mp18 and m13mp19 to sequence the amplified region. This allowed construction of the complete p58 cDNA containing 1680 bp. The original 1400 bp cDNA was also used to screen the MDBK cDNA library and pull another clone of 3140 bp containing the full coding sequence together with 5'- and 3'-UTRs.

Please replace the paragraph beginning on line 18 on Page 66 with the following:

Plasmids pM23 and pM226 (Miller & Hinnebusch, 1989, *Genes Dev.* 3, 1217) each carry a GCN4-lacZ fusion and genes necessary for plasmid selection and manufacture in *E. coli* and *S. cerevisiae*. These two plasmids differ by a single nucleotide: whereas pM23 has the two upstream open reading frames (ORF1 and ORF4) which together confer p68-sensitive regulation, mutation of the ORF1 ATG

codon leaves pM226 with only ORF4 which by itself confers constitutive, low level expression. In order to provide a T7 promoter for efficient *in vitro* transcription, the *Sal* I-*Bgl* II fragments of pM23 and pM226 are replaced with a PCR-generated fragment (PCR-1 or PCR-2, respectively) as follows. PCR-1 and PCR-2 are made using oligos T7-1 (5'gcg tcg act aat acg act cac tat agg gag TCT TAT ATA ATA GAT ATA CAA AAC (SEQ ID NO:32), with lower case for a *Sal* I recognition site and the T7 RNA polymerase promoter, and upper case for *GCN4* sequence starting with the 5' end of the native mRNA), and T7-2 (5' GGG AAA TTT TTA TTG GCG AGT AAA CCT GG (SEQ ID NO:33), residues 503 to 475, relative to the transcription start site) as primers, plasmids pM23 and pM226, respectively, as templates, and a standard GeneAmp™ PCR kit from Perkin Elmer. The PCR-generated fragments are cloned directly using the TA-cloning kit from Invitrogen. The promoter fragments are excised with *Sal* I and *Bgl* II and subcloned into pM23 and pM226, respectively, that have been digested with the same two enzymes.

Please replace the paragraph beginning on line 9 on Page 88 with the following:

The sequence of the 5'-UTR is AGCAAAAGCAGGGUAGAUAAUCACUCACUGAGUGACAUCAAAAUC (SEQ ID NO:18). The 12 nucleotides underlined are conserved in all influenza mRNAs.

Please replace the paragraph beginning on line 26 on Page 147 with the following:

Applicant has designated antisense deoxyoligonucleotides that target the 3' end of the rhinovirus IRES element and inhibit rhinovirus IRES-dependent translation. This region of the IRES was chosen since it contains both the "Y_nX-$_m$AUG" motif and the conserved 21 base sequence described above and shown in Figure 1. Antisense deoxyoligonucleotide inhibition of the rhinovirus IRES element was assayed using the [^{35}S]-methionine incorporation assay (Figure 7) and luciferase activity assay (Figure 8). An example of an antisense oligonucleotide that targets this region is anti-IRES-oligo, which anneals to nts 518-551 of the rhinovirus 14 IRES. The sequence of anti-IRES-oligo (SEQ ID NO:[26] 10) is 5' AGTAGTCGGTCCCGTCCCGGAATTGCGCATTACG 3'

In the **Claims**:

Claim 3 (Currently Amended) A method of screening for an anti-viral agent[, comprising], said method comprising:

(a) contacting a test agent with an RNA comprising a Hepatitis A virus IRES operably linked to a reporter-encoding sequence and,

(b) assessing the activity of said reporter;

wherein a reduction in activity of said reporter in the presence of said agent as compared to in the absence of said agent indicates that said agent is an antiviral agent.

The Terminal Disclaimer filed 11/13/03 is acceptable and has been entered.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Guzo
February 2, 2004